DOCUMENTATION PAGE

Form Approved
OMB No 0704-0188

1b RESTRICTIVE MARKINGS	
2b DECLASSIFICATION / DOWNGRADING SCHEDULE	3 DISTRIBUTION / AVAILABILITY OF REPORT DISTRIBUTION STATEMENT A Approved for public release; Distribution Unlimited
4 PERFORMING ORGANIZATION REPORT NUMBER(S)	5 MONITORING ORGANIZATION REPORT NUMBER(S)
6a NAME OF PERFORMING ORGANIZATION New Jersey Institute of Technology	6b OFFICE SYMBOL (If applicable)
6c ADDRESS (City, State, and ZIP Code) Chemistry Division 323 King Boulevard Newark, NJ 07102	7a NAME OF MONITORING ORGANIZATION 7b ADDRESS (City, State, and ZIP Code)
8a NAME OF FUNDING / SPONSORING ORGANIZATION Office of Naval Research	8b OFFICE SYMBOL (If applicable) ONR
8c ADDRESS (City, State, and ZIP Code) 800 N. Quincy Street Arlington, VA 22217-5000	9 PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER 10 SOURCE OF FUNDING NUMBERS

PROGRAM ELEMENT NO.	PROJECT NO.	TASK NO.	WORK UNIT ACCESSION NO.

11 TITLE (Include Security Classification)
Molecular Modeling Studies of Cholic Acid Host: Shape and Dimensions

12 PERSONAL AUTHOR(S)
Suzanne M. Evans and Carol A. Venanzi

13a TYPE OF REPORT	13b TIME COVERED	14 DATE OF REPORT (Year, Month, Day)	15 PAGE COUNT
	FROM _____ TO _____	April 18, 1990	12

16 SUPPLEMENTARY NOTATION

17 COSATI CODES			18 SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	
07	03		

19 ABSTRACT (Continue on reverse if necessary and identify by block number)

The literature of sugar binding proteins, in particular the protein binding L-arabinose, indicates that the binding pocket shape is cup-like, with the hydroxyl groups of the L-arabinose hydrogen bonding to the ionized amino acids of the protein through the heteroatoms, with or without an intervening water network (Fig.1) Measurements of the L-arabinose binding protein cavity, taken from the computer graphics representation of the X-ray crytallographic coordinates, indicate that the cavity is approximately 12-12.3 A long and 7.3 A wide (Fig. 2). To evaluate the dimensions of a cavity created by two cholic acid molecules linked together by a substituted aromatic spacer, several starting structures for this "cup" or "clam" shape of the host system were generated. The study of this host system considers both the torsional angles of the cholic acids' side chain and the torsional angles linking the carboxamide group of the cholic acid molecule to the benzyl group..

20 DISTRIBUTION / AVAILABILITY OF ABSTRACT	21 ABSTRACT SECURITY CLASSIFICATION
☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS	Unclassified

22a NAME OF RESPONSIBLE INDIVIDUAL	22b TELEPHONE (Include Area Code)	22c OFFICE SYMBOL
Harold E. Guard	(202) 696-4402	ONR

DD Form 1473, JUN 86 — Previous editions are obsolete. — SECURITY CLASSIFICATION OF THIS PAGE

Office of Naval Research
Contract N00014-88-K-0472
R T Code 413p008

Technical Report No. 3

Molecular Modeling Studies of Cholic Acid Host: Shape And Dimensions

by

Suzanne M. Evans* and Carol A. Venanzi

New Jersey Institute of Technology
Chemistry Division
Newark, NJ 07102

April 18, 1990

*: The BOC Technical Center, Murray Hill, NJ

INTRODUCTION

The goal of this project is the design of an optimal receptor for glucose in nonpolar solvents. We are collaborating with Professor Cindy Burrows' synthetic group at SUNY, Stoney Brook. The first phase of the work involves analysis of the shape and dimensions of some of the cholic acid hosts which have been targetted by Professor Burrows' group for synthesis.

We compare the shape, dimensions, and potential hydrogen bonding interactions in the hosts to X-ray data for L-arabinose Binding Protein (Quiocho, et al) in order to evaluate the ability of the synthetic host to provide optimal hydrogen bonding interactions typical of the natural (Binding Protein) host.

Further work will involve molecular mechanics calculation of the host-guest complex for several hosts related by alteration in the size of the spacer groups between cholic acid fragments. The results will be used to identify optimal target hosts for synthesis.

The body of the report has been prepared by Ms. Suzanne Evans, The BOC Technical Center. Ms. Evans is working full-time at BOC and pursuing a Ph.D. in chemistry part-time at Rutgers University, Newark, under my supervision. This complex arrangement is due to the fact that NJIT does not have a Ph.D. program in Chemistry.

The Cholic Acid Host System Shape

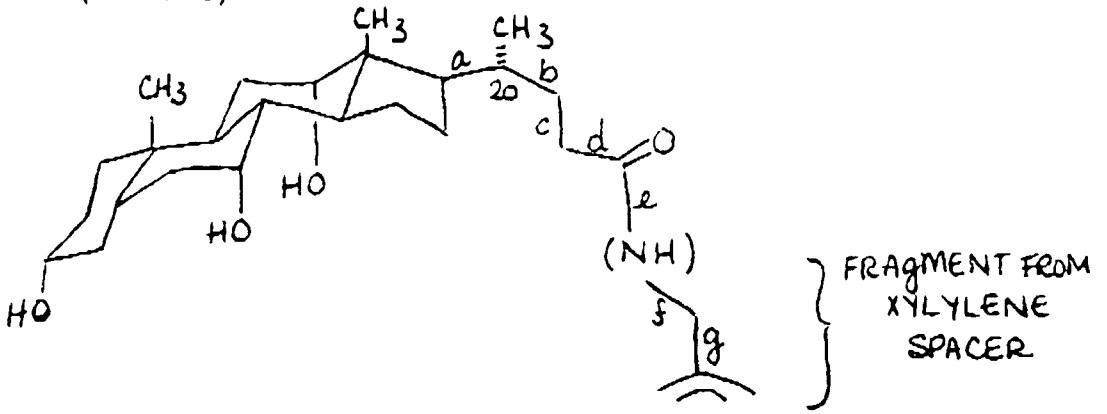
Abstract

The literature of sugar binding proteins, in particular the protein binding L-arabinose, indicates that the binding pocket shape is cup-like, with the hydroxyl groups of the L-arabinose hydrogen bonding to the ionized amino acids of the protein through the heteroatoms, with or without an intervening water network (Fig. 1). Measurements of the L-arabinose binding protein cavity, taken from the computer graphics representation of the X-ray crystallographic coordinates, indicate that the cavity is approximately 12-12.3 Å long and 7.3 Å wide (Fig. 2). To evaluate the dimensions of a cavity created by two cholic acid molecules linked together by a substituted aromatic spacer, several starting structures for this "cup" or "clam" shape of the host system were generated. The study of this host system considers both the torsional angles of the cholic acids' side chain and the torsional angles linking the carboxamide group of the cholic acid molecule to the benzyl group.

The clam shape halves in the host system are not perfect mirror images in space, an observation which is initially puzzling, but explainable on a geometrical and stereochemical basis. The C_{20} chiral center in the cholic acid molecule is not represented by an enantiomeric pair (one enantiomer in the top half of the clam, opposite enantiomer in the bottom half), so that the clam halves will never be mirror images. In addition, since the cholic acid system is rigid, there exist no bond rotation possibilities in the ABCD rings which could create a "pseudo" mirror image. Therefore, the host shapes which result upon manipulation of the bonds joining the cholic acids to the aromatic spacer all have the top arm offset relative to the bottom arm of the clam. However, the general clam shape which results is quite flexible and thus sensitive to minor bond rotations, giving cavities of similar shapes but different widths.

The following torsional angles, obtained from crystallographic coordinates, were used for the choic acid section of the clam structure:

Degrees	a	b	c	d	e	f	g
X-TAL (BUGJES)	+173.6	+60.0	+179.3	-168.7	+172.6	+180.0	0



When the cholic acid molecule above was connected to m-xylylene as the aromatic spacer, modification of dihedral angle g was necessary to alleviate bad steric interactions between the hydrogen of N-H in the amide and the ortho-proton on the benzene ring (Fig. 3). Simple models of benzene rings containing an attached chain, found by searching the Cambridge Crystallographic Database, indicated that typical values for dihedral angle g would be -70 to -80 degrees or +150 degrees. In the cholic acid-spacer-cholic acid host system, a combination of positive and negative fixed angles g, g' (top and bottom half of the clam structure, respectively) gave the final clam shapes described below (Fig. 4,5):

Name	Torsional Angles°		NH--H_{ar} (Å)		Cavity Width (Å)
	g Top	g'Bottom	Top	Bottom	
_60 Clam	-60	+60	2.61	2.63	5.2--7.2 (overlap)
_90 Clam	-90	+90	3.37	3.39	8.7
_120 Clam	+120	-120	2.61	2.63	13.8
_150 Clam	+150	-150	1.86	1.89	18.5
MI of _150 *	+150	-150	1.86	1.89	Wrong Shape

*MI=total mirror image of dihedral angles a,b,c,d,e,f,g

Specific distances which characterize each cavity in the host system are:

Name	O12--O12 (Å)	O7--O3 (Å)	O12--O7(Å)
_60 Clam	4.67	10.39	8.49
_90 Clam	7.84	18.87	8.23
_120 Clam	11.86	15.72	15.28
__150 Clam	14.91	19.38	17.77
MI of _150	17.84	19.17	15.57

Three of the clam shapes seem satisfactory, although each is different in width. The _60 Clam structure is clearly too small in the interior and has the A-ring ends overlapping. However, the _90 Clam closely resembles the dimensions of the L-arabinose binding protein and provides a reasonable starting structure for docking the sugar guest. Slight manipulation of dihedral angle b was done to assess the effects on the cavity accompanying changes in the flexible chain. However, in the following two structures, a slightly different cholic acid crystal structure was used:

Name	b,b'°	NH--H_{ar} (Å)	Cavity	O12--O12	O7--O3	O12--O7
_MX2_60	+60.6	3.37, 4.99	8.54	7.45	9.92	8.12
_MX1_0	0,+60.6	3.37, 3.37	N/A*	6.56	5.04	5.24

*N/A = not applicable, overlapping ends

The +90, -90 degree torsional angle combination consistently provides relief of unfavorable hydrogen--hydrogen steric interactions and creates a cavity approximating that of L-arabinose binding protein. The additional change in torsional angles b, b' to the 0, +60.6 degree combination does not give a full cavity since the steroid ends (ring A) overlap.

For the p-xylylene aromatic spacer group, the clam shape seems more symmetrical due to the symmetrical substitution of the steroidal arms onto the benzene ring. In addition, the NH--H_{ar} interactions are not as severe. The

cavity formed from g,g'=-90, +90 with b,b' both equal to +60.6 degrees results in a very good size cavity , whose length is 12.3 Å and width in the middle is 6.47 Å (Fig 6.). This starting clam structure provides a cavity shape even closer to the L-arabinose binding cavity than that found using the m-xylylene spacer. In addition, changing torsional angle f from +180 to -180 in the bottom arm generates the extended form of the clam structure (Fig. 7), in contrast to the closed form (clam shape).

The study of the "clam" shape created by the m-xylylene and p-xylylene spacers is nearly complete. The next phase in the study of the cholic acid host-guest system is to evaluate the energies of the open (extended) and closed (clam) shapes and then to begin docking the sugar guests.

Suzanne M. Evans
25 February 1990

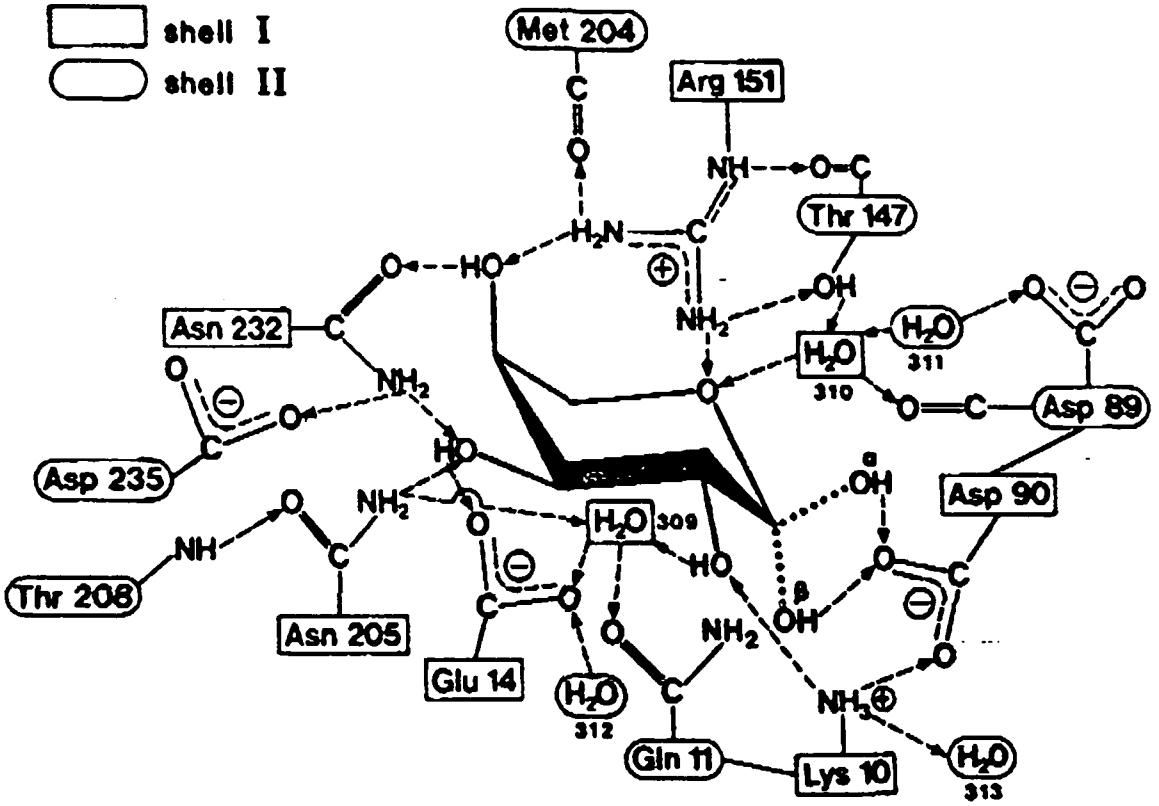


Figure 2. Schematic diagram of the intricate networks of hydrogen bonds formed in the complex of the L-arabinose-binding protein with the L-arabinose substrate. Shell I represents the essential residues hydrogen-bonded to the sugars and to adjacent second shell (shell II) of residues. Note especially that Arg-151 is not involved in salt linkages but is the source of five donor groups for five hydrogen bonds. (Adapted from Quiocho and Vyas 1984.)

FIGURE 1.

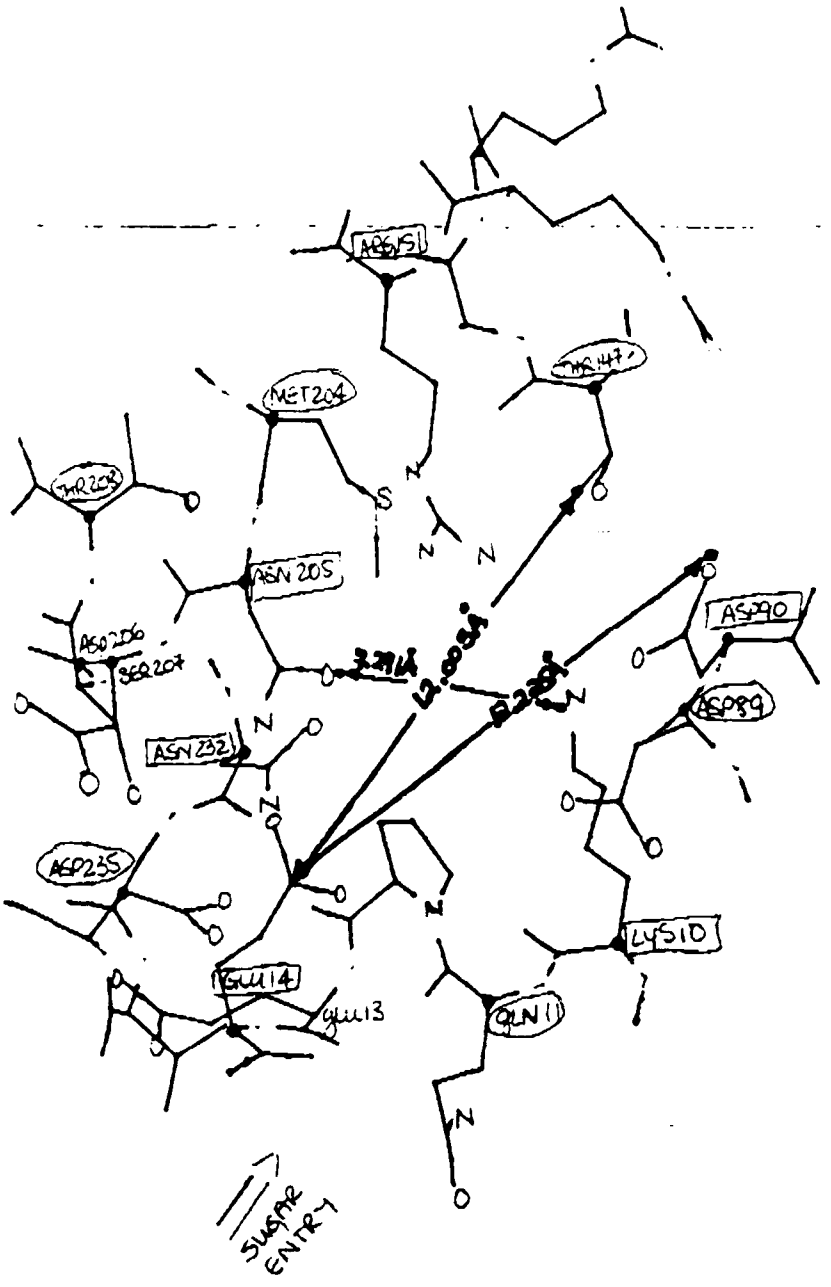


FIGURE 2.

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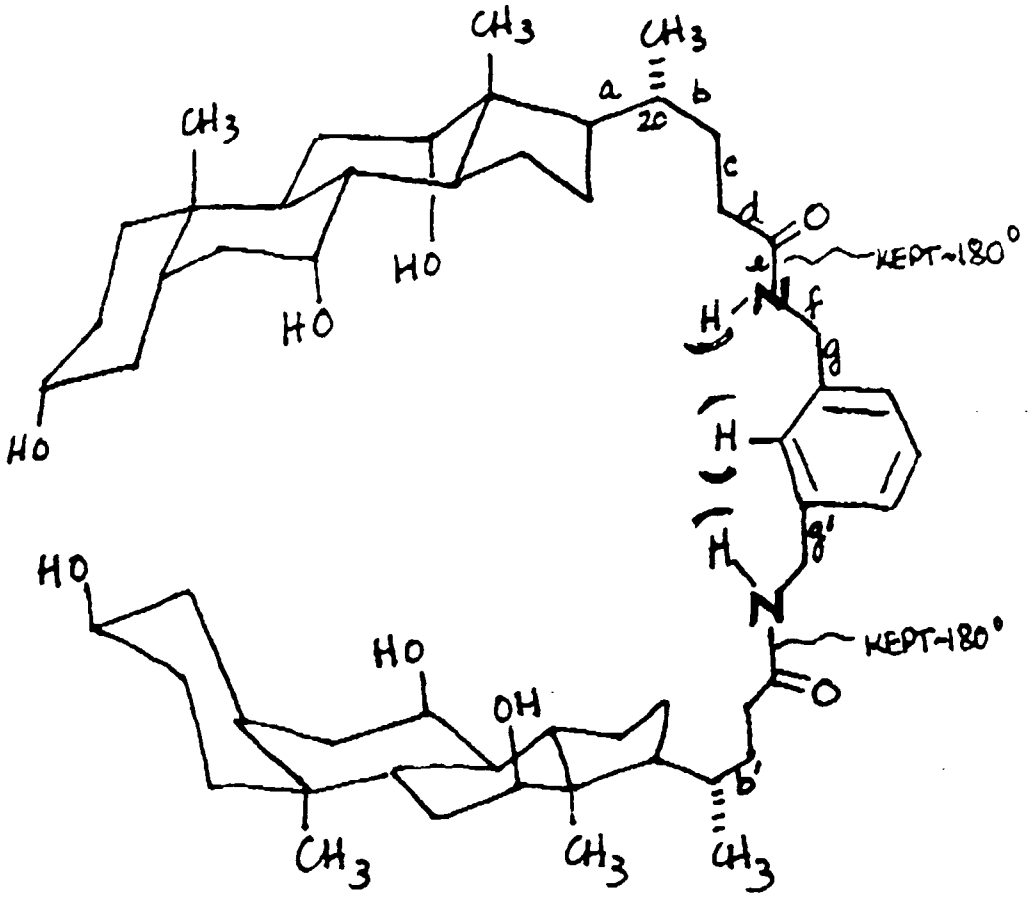
CH3
CH3
a
b
20
CH3
c
d
O
HO
HO
HO
KEPT-180°
e
N
f
H
g
H
g'
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N
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KEPT-180°
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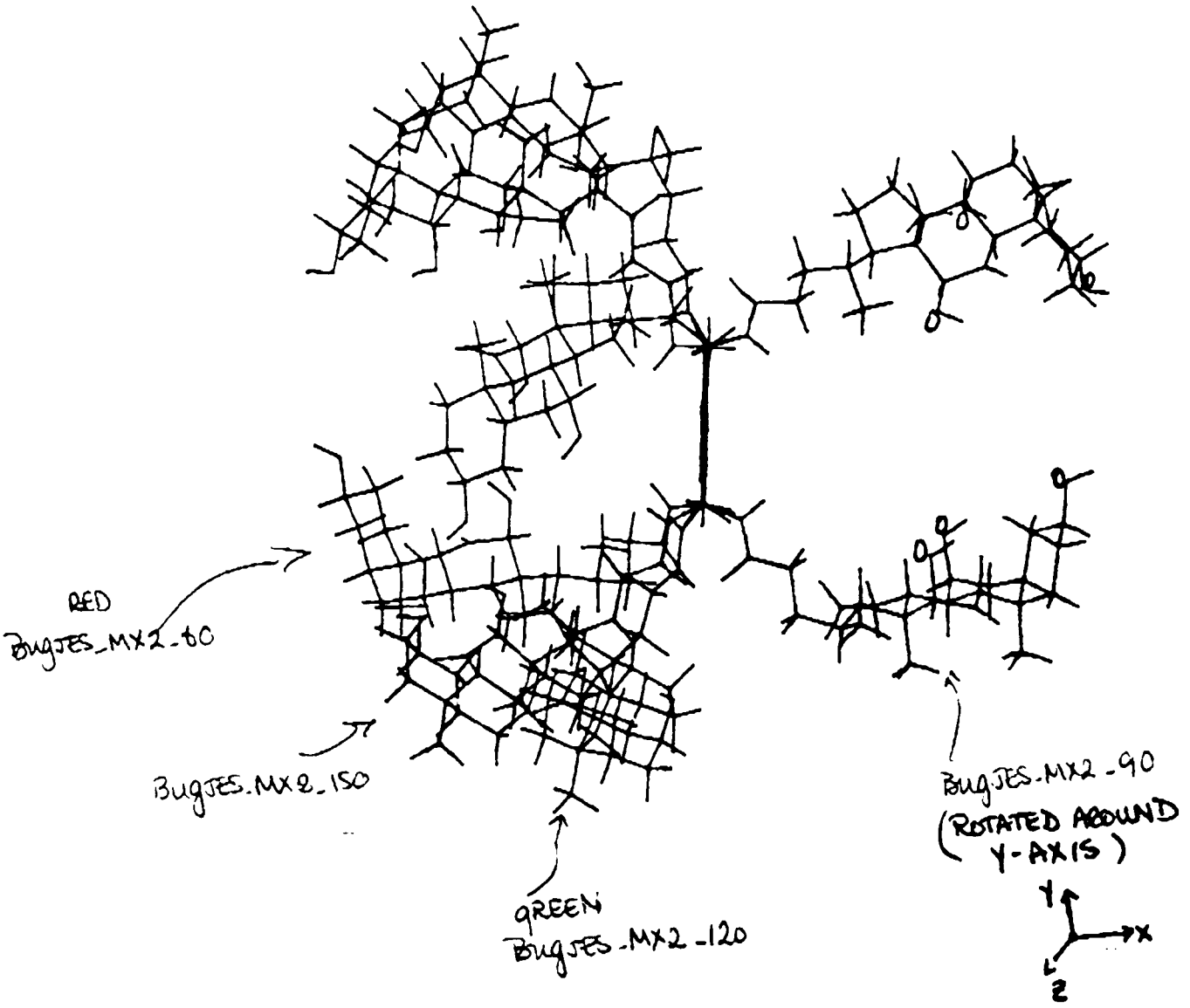
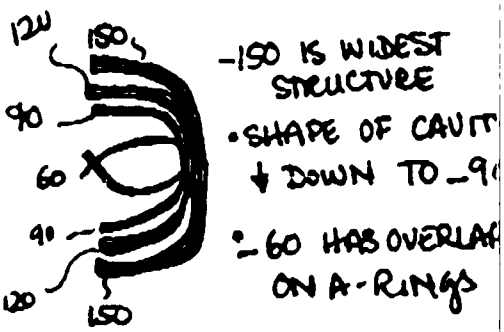
b'
CH3
CH3
CH3

FIGURE 3.

FIGURE 4.





BUGJES_MX2 4 CONFORMERS

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FIGURE 5.

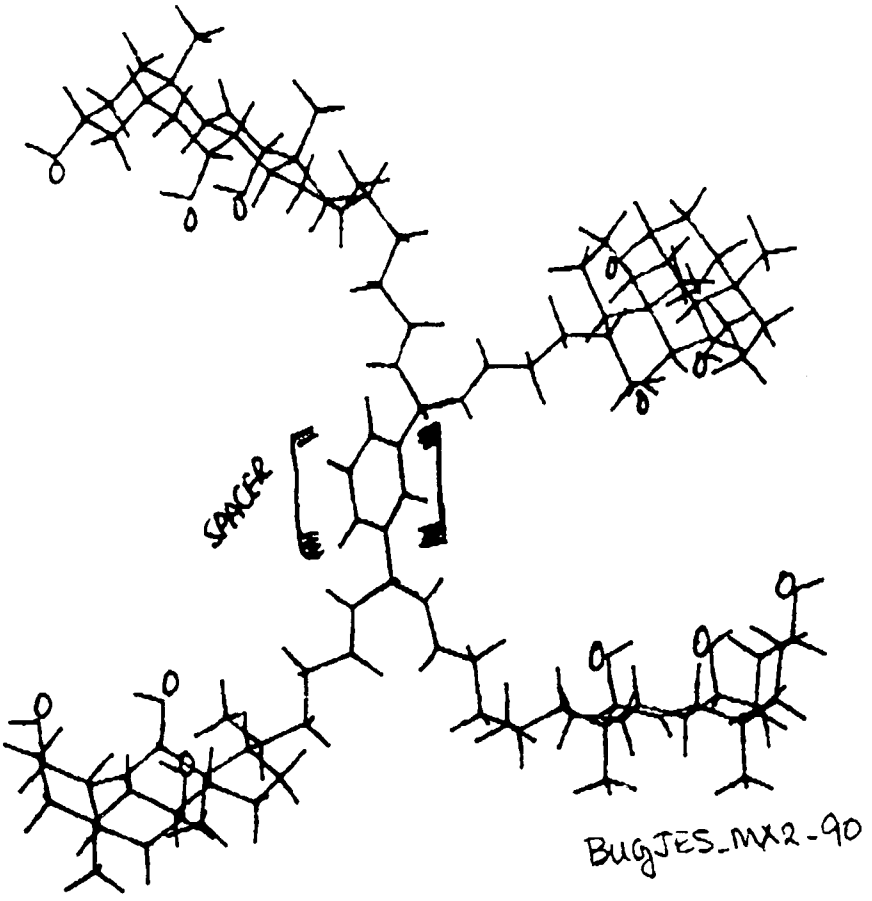

FIGURE 6.

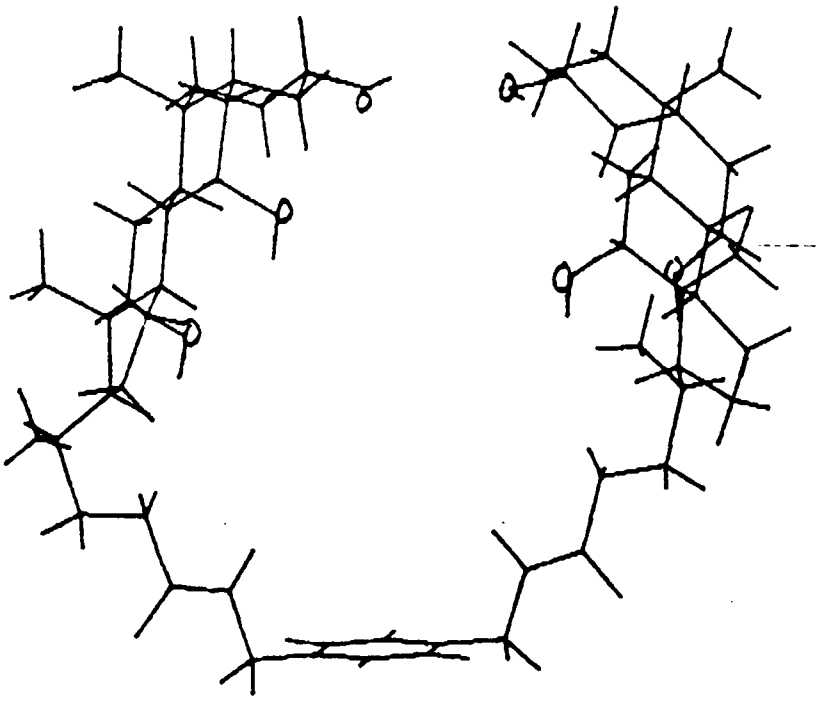

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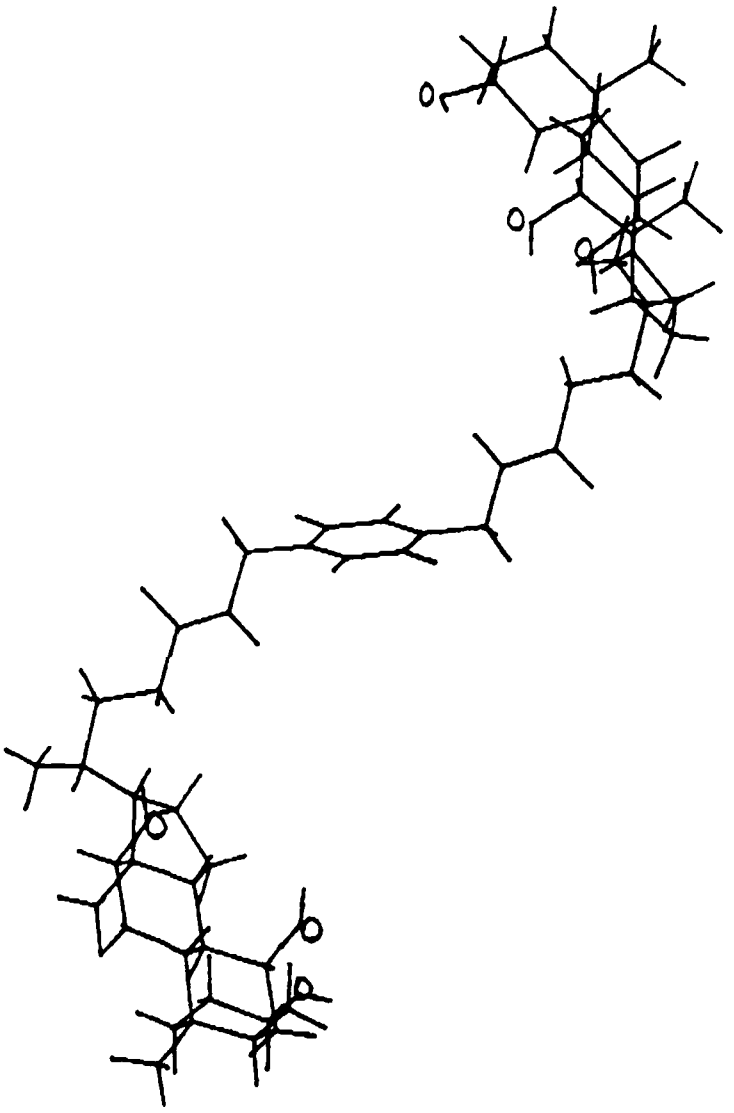
FIGURE 7.



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